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SYMPOSIUM

Glucocentric Metabolism in Ultra-Endurance Sled Dogs

Michael S. Davis [1]

Department of Physiological Sciences, College of Veterinary Medicine, Oklahoma State University, 264 McElroy Hall, Stillwater, OK 74078, USA

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[1]E-mail: michael.davis@okstate.edu

Foods were purchased in April 2017 through retail outlets and analyzed within a month of purchase by Nestle'-Purina Analytical Laboratories (St. Louis, MO). Total energy determined by bomb calorimetry. % Fat determined using acid hydrolysis, % Protein determined using the Kjeldahl method, % Starch determined by enzymatic methods, % Fiber determined using drying, ether-extraction, and acid and base-digestion, % Moisture determined through air-drying. Metabolizable energy (ME) determined using the Atwater method.

Synopsis The total energy expenditure of a racing sled dog can exceed 500 kcal/kg bodyweight during typical events spanning a week or more. Based on early research, as well as practical considerations, modern commercial diets are formulated to meet these energy requirements using fat and protein. However, more recent research provides a clear picture of a canine athlete with glucocentric metabolism, including many conditioning-induced adaptations oriented toward sustaining submaximal exercise with glucose as the primary metabolic fuel despite the consumption of fat as the primary dietary energy source. The specific strategies used by racing sled dogs to maintain a robust supply of glucose during exercise, as well as the possible role of fat in facilitating that metabolic priority, is the subject of ongoing research.

Introduction

Canine athletes have impressive exercise capacity, and their exercise physiology has received considerable attention by the biomedical research community, both as a model of basic mammalian adaptation to exercise as well as with a goal of improving the health, well-being, and performance of the dogs themselves. Specific breeds have been developed to perform specific tasks and the ability of a particular dog to perform those tasks is honed by physiological conditioning. The most widely studied instance of a specific breed being developed and conditioned for a specific exercise task is the ultra-endurance racing sled dog that competes in multiday races such as the annual Iditarod Trail International Sled Dog Race. Over three decades of scientific research has begun to shed light on the specific metabolic adaptations that permit teams of these dogs to race under some of the harshest environmental conditions in the world, and our evolving understanding of these unique athletes is challenging metabolic dogma in the field of mammalian exercise physiology.

Whole body exercise metabolism—calories burned, distances traveled

The most extensively studied canine athlete is the racing sled dog. These dogs, typically between 20 and 25 kg bodyweight, compete in teams of 12–16 dogs over race distances of 300–1000 miles while pulling a lightly loaded sled and a musher who will alternate between sitting, standing, or running behind and pushing the sled. In the typical race, the run-rest pattern is largely at the discretion of the musher who manages the activity of the team based on the trail conditions, race strategy, and the needs for food and rest. Daily travel distances during a race can range from 100 to 150 miles/day depending on the race, with the shorter 300-mile races typically won in approximately 2 days and the longer 1000-

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mile races won in approximately 9 days. The caloric expenditure during these races is substantial, with measured total energy expenditure of approximately 11,250 kcal/day during a 300-mile race that was completed in 50 h (Hinchcliff et al. 1997). In that study, caloric intake failed to match energy expenditure, resulting in moderate weight loss. In a study of multiday exercise at a pace selected to simulate a 1000-mile race (100 miles/day), dogs consumed an estimated 5000 kcal/day based on phantom meal testing and lost approximately 5% of their bodyweight over the 5-day study, indicating that caloric expenditure was considerably higher than intake (McKenzie et al. 2008). In another study of racing dogs, investigators estimated daily caloric expenditure of 8995–13,799 kcal per day during a 1000-mile race, based on analysis of daily caloric intake and concurrent weight loss (Loftus et al. 2014). By comparison, studies of Labrador Retrievers used by the United States Marine Corps for detection of concealed explosives expend up to 6000 kcal/day performing simulated 9-h patrols during which they covered 22 miles (Pratt Phillips et al. 2015). Although these dogs did not lose bodyweight during a 5-day study, downregulation of myocyte protein synthesis was detected, suggesting that conservation of body mass was at the expense of normal cellular maintenance (Miller et al. 2015). Overall, these studies (as well as the decades of experience of professional dog mushers) testify to the considerable myocellular energy consumption of a well-conditioned athletic dog, and beg the question: what is the metabolic physiology that supports this magnitude of sustained total energy expenditure?

Typical food

The metabolic strategy for fueling the exercise performance of ultraendurance sled dogs begins with their dietary intake. Simply stated, in order to sustain caloric expenditures of 9000–12,000 kcal/day, the dogs must consume dietary calories of at least a comparable magnitude since any shortfall will be met by consumption of body tissue. There are multiple practical and physiological considerations due to the considerable mass and volume of food required to supply 12,000 kcal/day. Food with high caloric density is ideal to minimize the overall volume that must be consumed in a single day of racing. For that reason, most commercial racing diets consist of kibble with more than 450 kcal/cup and more than 4000 kcal/kg metabolizable energy (Table 1). In order to achieve these calorie densities, as well as maintain sufficient palatability to permit voluntary consumption of the food, the diets contain 20–30% fat on a dry matter basis. These practical considerations are also supported by early nutritional research that recommended very high fat diets for ultraendurance sled dogs (Kronfeld 1973; Hammel et al. 1977; Kronfeld et al. 1977; Reynolds et al. 1995). The diets also contain a very high proportion of protein (30% or higher on a dry matter basis) due in part to research showing that very high protein intake in racing sled dogs promoted expansion of erythrocyte concentrations and low protein intake seemed to predispose the dogs to injury (Reynolds et al. 1999). These ingredients leave little room for carbohydrates, and the typical diet marketed for racing sled dogs contains only 10–15% carbohydrates in the form of starch (Table 1). Although considerable attention is sometimes paid to the feeding of meat products such as salmon, beef fat, and chicken or turkey skins, these products are seldom fed in sufficient amounts to represent more than 20% of the total caloric intake (Davis et al. 2018) and instead represent palatability aids to help ensure consumption of the kibble "stew" that is often fed throughout training and racing. Importantly, these products contain very little carbohydrate, instead being comprised of primarily fat and protein (and water in the case of muscle tissue). For example, salmon is typically ~70% water, 22% protein, 4% fat, and less than 1% carbohydrate, and beef fat/tripe is ~20% water, 8% protein, 70% fat, and less than 1% carbohydrate. Thus, the diets of high-performing athletic dogs would be considered "low-carbohydrate" diets.

Calorimetry and whole-body substrate flux

Calorimetry is the gold standard method for quantifying metabolic exercise intensity through the measurement of rates of oxygen consumption and carbon dioxide production. Sled dogs are likely the most extreme domestic animals in terms of maximal oxygen consumption, with LIGHTLY TRAINED dogs registering peak oxygen consumption of almost 200 mL/min/kg (Banse et al. 2007). It is likely that fully conditioned dogs have much higher values, but with those values come substantial technical challenges such as managing the corresponding metabolic heat production during a maximal aerobic capacity test. Additional information on metabolic strategy can be derived from these measurements, such as the respiratory exchange ratio (RER). The RER is the ratio between the rate of carbon dioxide production and oxygen consumption, and the specific value that is derived reflects the relative amounts of different oxidizable substrates that are

Table 1 Analysis of selected commercial foods marketed for racing sled dogs

Diet	Eagle 30/20	RedPaw 38	Caribou Creek Gold	Dr. Tim's Momentum	Royal Canin 4800
Total energy (kcal/gm)	5.15	5.36	5.29	5.57	5.53
% Fat	21.2	24.8	23.8	25.7	30.3
% Protein	32.1	39.3	36.1	37.9	31.1
% Starch	21.2	9.6	14.1	14.8	15.9
% Fiber	4.37	2.32	1.78	2.55	2.04
% Moisture	6.20	7.31	9.33	3.69	6.71
9000 ME kcal mass (g)	2228	2150	2169	2036	1954
9000 ME kcal starch mass (g)	472	205	306	301	311
9000 ME kcal protein mass (g)	715	845	783	772	608

being burned to power the exercise. A value of 1.0 (1 mole of CO_2 produced for every mole of O_2 consumed) reflects the combustion of carbohydrates and a value of 0.7 (1 mole of CO_2 produced for every 1.4 moles of O_2 consumed) reflects the combustion of fat. Although the measured RER can fall outside these boundaries during non-steady state conditions, steady-state values will fall between these boundaries and reflect the relative contributions of fat and carbohydrate combustion.

In general, it is expected that sedentary periods or periods of light exercise will be characterized primarily by the combustion of fat, with progressively higher contributions of carbohydrate as exercise intensity increases. Thus, it was somewhat surprising when calorimetry studies of racing sled dogs revealed a relatively high RER value (0.87 ± 0.01) while exercising at a relatively modest pace (10.5 km/h on a 4% grade, resulting in a VO_2 of 54.9 ± 2.1 mL/kg min) (Miller et al. 2015). This pace was maintained at a slow trot, often referred to as a "survival trot" by mushers because dogs using this gait and speed can maintain it without interruption for 8–10 h under virtually any conditions, so it was very surprising that it was fueled primarily by carbohydrate. It was even more surprising that in response to a full season of endurance conditioning, the same exercise resulted in an INCREASE in relative carbohydrate reliance (RER $= 0.92 \pm 0.01$). In the same study, isotopically labeled glucose was infused during the exercise test and analysis of the relative changes in enrichment of both blood glucose and expired breath CO_2 found that the dogs were oxidizing approximately 40 mg/kg/min of glucose during the exercise test in the unconditioned state, and this increased to nearly 60 mg/kg/min in the conditioned state for the same exercise task. This finding stands in stark contrast with numerous studies of human and equine endurance athletes, in which increases in fitness for endurance exercise result in a relative DECREASE in the utilization of carbohydrates at moderate exercise intensities. It also raises numerous questions, not the least of which is: where is all that glucose coming from?

The macronutrient ratios in the diet are closely related to the RER of the subject consuming the diet and in principle can predict the long-term RER if the "system" remains sufficiently closed and stable. As described earlier in this review, the typical diet of a racing sled dog has a relatively high fat content. Using formulas of Jequier et al. (1987) for calculating the food quotient (i.e., the predicted production of oxygen and carbon dioxide resulting from the protein, fat, and carbohydrates in the diet), we found that the typical diet of racing sled dogs has a food quotient of approximately 0.78—far lower than the RER measured in our studies of moderately-exercising dogs. If it is assumed that a racing sled dog consumes approximately 9000 metabolizable energy kilocalories of a typical diet formulated for racing sled dogs, the dogs will consume approximately 300 g of glucose/day (primarily in the form of dietary starch) (Table 1) but will burn more than 800 g of glucose/day (assuming 50 mg/kg/min, 23 kg dog, and 12 h/day of running at 10 km/h). Clearly, dietary carbohydrate intake is insufficient to support the magnitude of glucose oxidation that has been reported in these dogs. Alternative sources of glucose must be present if the substrate oxidation patterns that have been reported are maintained throughout the typical sled dog race.

Hormonal responses and hepatic glucose output

The increased energy expenditure of skeletal muscle during exercise represents not just a metabolic stress to the muscle, but to the entire dog. In the broadest sense, the exercising dog moves to a negative calorie

balance almost instantaneously, and the homeostatic systems that manage energy stores must respond accordingly. As a result, sustained exercise results in changes in circulating hormone concentrations that collectively are directed at increasing availability of extramuscular substrates to the working muscle. As originally documented by Wasserman and Cherrington (1991) in laboratory hounds, the onset of exercise results in a decrease in insulin secretion, and an increase in secretion of glucagon, cortisol, and epinephrine, as well as selective activation of the sympathetic nervous system. The decrease in insulin secretion decreases hepatic uptake of glucose from the portal circulation, stimulates hepatic glycogenolysis, and increases sensitivity of hepatocytes to glucagon, resulting in a net increase in hepatic glucose output (Wasserman et al. 1989). Decreased circulating insulin also removes the inhibition of hormone sensitive lipase, allowing the breakdown of stored triglycerides in adipose tissue and releasing non-esterified fatty acids and glycerol into the systemic circulation. The increase in glucagon secretion is critical for full activation of hepatic glucose output through a combination of glycogenolysis and gluconeogenesis (Wasserman et al. 1989). Under the combined influences of low insulin and high glucagon, hepatic glucose output can rise from approximately 3 to 9 mg/kg/min during the initial exercise period in modestly trained mixed breed hounds exercising at 6 km/h on a 12% grade (Wasserman and Cherrington 1991). Similar rates of glucose appearance and concurrent disappearance were recorded in sled dogs exercising at a comparable intensity (faster pace, lower incline) for a similar amount of time (Miller et al. 2015). When these values are compared with the overall rate of glucose oxidation, it is clear that intracellular glucose stores (i.e., glycogen) are the primary source of glucose, at least during the initial stages of submaximal exercise. This conclusion is supported by measurements of muscle glycogen depletion following 12 h of exercise at a comparable intensity in racing sled dogs (McKenzie et al. 2005, 2008).

The rate of hepatic glucose output likely increases with increased exercise duration. The ratio of glucagon to insulin has been proposed as a relative indicator of stimulation of hepatic glucose output through all mechanisms (Wasserman and Cherrington 1991), and in the studies of exercising mixed-breed hounds, the *G*/*I* ratio at the end of a 150 min exercise session was increased approximately four-fold over resting baseline (Wasserman et al. 1987, 1989). By comparison, a study of racing sled dogs reported that the *G*/*I* ratio increased nearly 16-fold after a single day of exercise and more than 20-fold after 4 days of prolonged submaximal exercise (Davis et al. 2020). These increases in the stimulus for hepatic glucose output correspond to a marked shift in the utilization of muscle glycogen—a rapid transition from a glycogen-depleting phenotype to completely glycogen sparing. If the dogs do not concurrently shift away from burning carbohydrate, then hepatic glucose output would have to increase five-fold in order to completely replace intramuscular glycogen as a source of glucose for oxidation. Although there are not currently data to confirm that the dogs have the hepatic glucose output to completely replace the same rate of utilization of intramuscular glycogen, the five-fold increase in stimulation of hepatic glucose output supports the contention that racing sled dogs replace muscle glycogen utilization with hepatic gluconeogenesis.

Additional support for a robust, glycogen-sparing increase in hepatic gluconeogenesis can be found by considering direct and indirect measurements of gluconeogenic precursors. Dogs produce modest amounts of lactate during submaximal exercise, but neither studies in mixed-breed hounds nor sled dogs concluded that lactate was a major substrate for hepatic gluconeogenesis. However, glycerol produced during lipolysis can be used for gluconeogenesis and the rate of glycerol disappearance from the blood stream—either to be oxidized directly or used for gluconeogenesis, was significantly increased by exercise in racing sled dogs. However, the most robust supply of gluconeogenic substrates is likely circulating amino acids. Circulating amino acids, whether from dietary protein or endogenous protein catabolism, are removed from the portal circulation by the liver. Doubling of circulating glucagon resulted in an increase from approximately 25% to approximately 60% of portal alanine being extracted by the liver. The effect of further increases in glucagon, such as the increase reported for racing sled dogs (Davis et al. 2020), is not yet known, but it is possible that even high rates of amino acid extraction by the liver occur in these dogs. Certainly, increases in serum urea concentrations during prolonged multiday exercise provide compelling evidence of a large magnitude of urea production (McKenzie et al. 2007). The degree to which this urea production is secondary to hepatic gluconeogenesis is unknown, but collectively the evidence supports the idea that a substantial fraction of dietary protein (of which there is over 700 g in a 9000-kcal diet of racing dog kibble) (Table 1) is actually used for gluconeogenesis. Additionally, it is likely that body tissue protein is an important source of

gluconeogenic precursors under the influence of a modest increase in serum cortisol (Davis et al. 2020).

Insulin sensitivity

Quantification of insulin sensitivity can provide some clues as to the metabolic strategies used by racing sled dogs. Insulin-stimulated uptake of glucose into skeletal muscle shares many of the same pathway elements as contraction-mediated increases in transarcolemmal glucose transport, particularly the sensitivity of glucose transporter translocation and the number of available glucose transporters available for expression on the sarcolemma. Regular exercise and increased fitness is often prescribed to people with low insulin sensitivity as a relatively consistent strategy for increasing their capacity for insulin-stimulated clearance of blood glucose into insulin sensitive tissues such as skeletal muscle, liver, and adipose tissue. Increases in insulin sensitivity in people with normal values through increased athletic fitness are less consistent, but there is a consensus that if the fitness program is sufficiently robust and tailored toward improving endurance, increased insulin sensitivity can be expected. Thus, it is no surprise that racing sled dogs demonstrate increased insulin sensitivity in response to a season of athletic conditioning. In a study using euglycemic hyperinsulinemic clamps to quantify insulin sensitivity, unconditioned (but previously conditioned) racing sled dogs had insulin sensitivity values that were 20–50% higher than values obtained from mongrel dogs using a similar protocol (Pratt Phillips et al. 2014). Perhaps due to this remarkably high level of insulin sensitivity in the unconditioned (basal) state, routine conditioning did not result in a change in insulin sensitivity, but a substantial exercise challenge (440 miles in 3.5 days) was sufficient to cause a 75% increase in insulin sensitivity. In a second study in which insulin sensitivity was quantified using a frequent-sampled intravenous glucose tolerance test, unconditioned dogs similarly had a high value for basal insulin sensitivity (more than double that of previously published studies of sedentary dogs) and a 250% increase in insulin sensitivity in response to conditioning (Davis et al. 2018). Moreover, the study reported a 150% increase in insulin INDEPENDENT glucose clearance—a remarkable finding when one considers that the whole-body rate of insulin independent glucose clearance appears to be highly conserved across mammalian species regardless of fitness. In fact, the study of highly conditioned sled dogs represents one of the only publications in which the rate of insulin independent glucose clearance has deviated from the "normal value" of 3–4% per minute. Combined, these studies provide supportive evidence for the conditioning-induced development of a robust capacity for moving glucose from the blood stream into peripheral tissues. While it is logical to presume that skeletal muscle would be the tissue most likely to respond to exercise conditioning, studies of whole-body insulin sensitivity do not provide definitive evidence of the specific role of working muscle in peripheral glucose clearance.

Muscle changes transporters, sensitivity, gain

Evidence for the specific role of skeletal muscle in the robust capacity for peripheral glucose clearance in exercising sled dogs comes from studies of the muscle tissue. The same transporters that translocate from the cytoplasm to the sarcolemma in response to myocyte stimulation by insulin will also translocate to the sarcolemma in response to sustained contraction. In principle, the relative responsiveness of the muscle can be assessed using a standardized exercise test combined with some method of assessing glucose transport. To specifically assess muscle contribution to exercise-induced changes in substrate flux, we conducted a study using a standardized exercise test as a repeatable, quantifiable stimulus for contraction-mediated transporter expression and immediate post-exercise muscle biopsy to produce giant sarcolemmal vesicles (Davis et al. 2014). Skeletal muscle biopsies were obtained within 10 min following a 30-min treadmill exercise challenge (or rested controls), and the giant sarcolemmal vesicles created using these biopsies were exposed to radiolabeled glucose and palmitate to quantify relative transport capacity of these substrates across the sarcolemma. In the unconditioned state (after 4–5 months without compulsory exercise), there was no effect of exercise on sarcolemmal transport capacity of either glucose or palmitate. However, after a typical 7-month athletic conditioning program, both basal and exercise-stimulated glucose transport was increased (approximately three-fold and six-fold, respectively) compared with the unconditioned state, and exercise resulted in significantly greater glucose transport capacity compared with rested dogs. A qualitatively similar pattern was found for palmitate transport, but the magnitudes of the increases were substantially smaller. The increase in the basal (non-exercised) glucose transport corresponds well with the increased insulin-independent glucose transport found in the previous studies using the FSIGTT, and the increase in contraction-stimulated glucose

transport similarly agrees well with the increase in insulin-mediated glucose clearance. Importantly, the fact that the exercise challenge resulted in an increase in glucose uptake in the conditioned dogs, but not in the unconditioned dogs, demonstrated increased gain of contraction-mediated expression of glucose transporters on the sarcolemma.

GLUT4 is the primary insulin- and contraction-responsive transporter in skeletal muscle, and thus it would be expected that increased capacity for glucose transport would be associated with increased sarcolemmal expression of GLUT4. However, western blots of the giant sarcolemmal vesicles found that instead of increased localization of GLUT4 on these vesicles, the increased glucose transport was associated with DECREASED detection of GLUT4 (Davis et al. 2014). These results, as well as the increase in basal (unstimulated) glucose transport, suggested that other glucose transporters may be upregulated in the skeletal muscle of highly trained racing sled dogs. Recent unpublished data confirm this, with increased skeletal muscle expression of novel insulin-responsive glucose transporters as well as transporters that are constitutively expressed on the cell membrane of other tissues. These novel transporters may help explain the substantial increase in the capacity of racing sled dog skeletal muscle to take up glucose—a capacity so potent that they can replenish and even supercompensate their muscle glycogen stores while exercising (McKenzie et al. 2005, 2008).

Myocellular calorimetry

The purposeful adaptation of racing sled dogs to glucose as the preferred exercise fuel even extends to the subcellular level. In a study using high-resolution respirometry, conditioning of sled dog skeletal muscle increased its aerobic capacity when measured using intermediates of the citric acid cycle (pyruvate, glutamate, and malate) as substrates (Miller et al. 2017). However, its capacity to support aerobic respiration using β-oxidation of fatty acids actually decreased with conditioning. Thus, it is unlikely that sled dogs are switching to combustion of fatty acids in the muscle during their rapid development of a glycogen-sparing phenotype (McKenzie et al. 2005, 2008). Nevertheless, fatty acids likely play a role in the use of glucose as the preferred fuel for canine skeletal muscle. Recent analysis of samples from one of the sled dog multiday exercise studies found patterns of serum acylcarnitine concentrations supporting the premise that long- and perhaps medium-chain fatty acids actually serve as carnitine shuttles during exercise in sled dogs (Tosi et al. under review). Under this hypothesis, the primary site of fatty acid β-oxidation is actually in the liver, where the acetyl groups are exported as ketones and acetylcarnitine to be burned by skeletal muscle. Utilizing long-chain fatty acids to transport carnitine from the muscle back to the liver for synthesis of acetylcarnitines serves a second purpose of reducing the intracellular accumulation of fatty acids which can interfere with cellular respiration of glucose. This hypothesis requires further investigation.

Conclusions

There is little doubt that racing sled dogs possess the most potent metabolic machinery of the domestic animal kingdom when it comes to the ability to perform endurance exercise. Yet, we have an incomplete understanding of exactly how the dogs support their considerable daily energy expenditure on a diet that is predominantly made of fat and protein, but with skeletal muscles that seem to have a strong preference for burning glucose. Further investigations will no doubt continue to bring clarity to this issue, both to the benefit of the dogs that race long distances as well as the biomedical community at large. Despite the unanswered questions that currently remain, it is widely believed that the knowledge gained from the detailed investigations into sled dog nutrition and metabolism have resulted in both improved performance and improved health of these dogs, and that similar efforts directed toward other working dog populations would similarly result in benefits to these groups of dogs.

Conflict of interest statement

The author declares no conflicts of interest.

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